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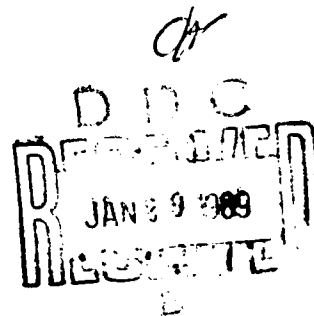
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DEPARTMENT OF THE ARMY
Fort Detrick
Frederick, Maryland

On the connection between hyaline and amyloid degeneration in the spleen.

by H. Stilling.

Virchow's Archives, 103: 21-38 (1886).

The question, whether specific tissue cells are the seat of amyloid degeneration, or whether the amyloid substance develops between them, has caused vigorous debate among pathological anatomists in the last decade. The renewed study of amyloid organs has led to important detailed results; the discussion has not resulted in new perspectives on the recognition of the inherent nature and origin of amyloid.

According to Virchow (1), the peculiarity of the process lies in infiltration, a gradual penetration of the parts with a substance which is added to them from without.

Others, however, claim that a local degeneration of the tissue elements is involved, although effected by general causes, and that amyloid is formed from its protoplasm (2).

Does it develop in the organism from the start with its characteristic peculiarities, or is the waxy process preceded by other alterations of the parts?

Virchow and Kyber (3) claim that the origin of amyloid is attributable to the combining of a substance circulating in the blood under normal conditions, with the protein substances of tissues with a reduced nutritional intake.

Cohnheim (4) speaks of a transitional stage between common and amyloid protoplasm.

Is it therefore probable that amyloid degeneration represents the final result of several successive metamorphoses, that amyloid is a mixture or compound of several substances? Which is the anatomical symptom of the original change, and which substance is the stage preceding amyloid?

V. Recklinghausen has answered this question with respect to hyaline degeneration.

Hyaline and amyloid, he says, only represent different stages in an identical transformation of tissue elements, and not products of degeneration which are of different nature. For their reactions are changeable to a certain degree, both have numerous morphological properties in common, both occur side by side (5).

Billroth (6), in connection with his presentation of amyloid degeneration of lymph glands, mentions that, in addition to amyloid epithelial cells, he found some with the same appearance which did not take the iodine and iodo-sulfuric acid reactions.

Beckmann (7) and Virchow (8) describe the transformation of a common colloid goiter into a struma amyloides.

Recently, Raehlmann (9) found hyaline masses next to amyloid in so-called amyloid tumors of the conjunctiva.

Grawitz (10) describes a chronic fibrous proliferation of the mucous membrane with amyloid degeneration of the mucus glands, the connective tissue fibers and the vascular walls from the nose and trachea of a horse, in which hyaline aggregations were also seen and sclerotic trabeculae were observed; the latter frequently appeared partly hyaline, partly amyloid.

Ziegler (11) reports a peculiar case.

A 50-year-old woman who died of heart failure revealed innumerable nodules and diffuse thickening of the serous membranes, in addition to amyloid degeneration of all mucous membranes, the tongue, the heart and lungs. The nodules and indurations consisted of a uniformly homogenous tissue or of homogenous epithelium. Part of them gave the amyloid reaction, others did not.

Zahn (12) has just published the description of a fibroma and osteofibroma of the tongue, in which some sections of the neoplasm and the preformed tissue showed hyaline as well as amyloid degeneration.

Even if these and similar observations (13) indicate that hyaline and amyloid degeneration may have parallel courses, they do not suffice to support the theory that the former is a preliminary stage of general amyloid degeneration.

In my opinion, the following factors are necessary for such proof:

First it must be shown that in most new cases of amyloid degeneration, hyaline parts and intermediate stages are also present.

Secondly, it must be established that the well-known chronic affections which usually include the waxy degeneration of the organs, also cause their hyaline deterioration and that the latter takes the former's place in cases where the duration of the affliction is shortened by an intercurrent disease. —

In striving for the indicated goal, the precise study of the spleen seemed especially fruitful, since as a rule it is initially beset by amyloid degeneration, as witnessed by Cohnheim (14) and a statistical summation by Henning (15).

I could, therefore, anticipate the easiest observation of the earliest start of the change at this point.

I have always examined the fresh organ first, then pieces hardened in alcohol, since Virchow's reaction may not be used as advantageously in connection with other modes of preservation. The fact that in the final analysis only the reaction of the parts to iodine and iodo-sulfuric acid is able to indicate amyloid or hyaline matter, needs no discussion.

Boettcher's (16) and Kyber's (17) rules should be followed for best results.

The thin sections in a weak iodine solution (iodine 0.25, potassium iodate 0.5, distilled water 100.0) are agitated with a needle until the iodine-red color is distinctly visible at the amyloid sites. They are then transferred to sulfuric acid of very low concentration (sulfuric acid 2.0, distilled water 100.0) and examined in this fluid or in glycerol. It is to be observed in this connection that the change in color evoked by sulfuric acid usually does not immediately reach its peak, that it commonly improves in the following days.

I have not used methyl violet, since it is extremely unreliable. Kyber (18) got a distinct red stain with it in the case of ordinary thyroid gland colloid, and urinary casts from non-amyloid kidneys, while he was unable to cause a reaction in masses which later proved to be amyloid upon addition of iodo-sulfuric acid.

Since it is of undeniable advantage in the study of organs with amyloid degeneration, if, in addition to the deteriorated parts, the normal tissue could also be differentiated by a vivid dye, I have tested a number of other coal-tar stains. Iodine green, containing iodine in the form of iodo-methyl, is quite useful.

It has all the advantages which Curschmann (19) ascribed to methyl green (never quite accepted), in which iodo-methyl of iodine green has been replaced by chloro-methyl in the interest of less expensive manufacture.

I use a solution of 0.5 stain to 150.0 units of distilled water, in which the fresh sections or those taken from alcoholic preparations are left for 24 hours. They are then simply washed off with distilled water. While the stain disappears, a red-violet coloration of the amyloid masses gradually appears, vividly contrasted against the green of the remaining tissue. The hyaline parts of the arteries appear blue, the hyaline lumps within the follicles, unstained. The preparations may be stored for several months in glycerol without changing. Alcohol rapidly removes the color and eradicates the differences obtained in staining.

Objects conserved in Mueller's fluid also show the reaction described if they are carefully dehydrated prior to staining.

These few data show that the use of iodine green is simpler than that of methyl violet; and concerning the main point, the positive reaction, I can attest after numerous tests, at least in the case of the spleen, that iodine green yields the same result as treatment with iodine and iodo-sulfuric acid, and that it definitely deserves preference over methyl violet, methyl green and safranine.

Special agents are hardly necessary for the differentiation of hyaline, which is so conspicuous. If necessary, the treatment of the tissue with diluted acids or a stain mentioned by von Recklinghausen (20), e.g. carmine, suffices.

The treatment of preparations with a weak iodine solution also yields good results, if a nucleic stain with alum carmine is first effected. The hyaline masses appear a shining yellow. Unfortunately, preparations of this kind cannot be preserved for longer periods.

Lately I have used orange, which normally is not practicable. This stain does not contrast the hyaline tissue from the remaining connective tissue substance as well as the agent described, but it is quite practicable for double stains due to its light basic color and the facility with which it may be combined with all sorts of nucleic stains. It is best used in very weak solutions (0.1: 150.0 distilled water); the preparations may be stored in glycerol or balsam.---

I have chosen the following observations from the material tested by me.

The spleen of a young woman who died of pulmonary tuberculosis and chronic dysentery was considerably enlarged, pale, slightly flaccid but still of considerable consistency. The follicles appeared very indistinctly. Upon treatment with iodine solution, isolated red spots and streaks were noted, but microscopic examination showed that the amyloid degeneration had progressed further than was visible to the naked eye.

The median arteries and Malpighi's bodies are involved.

In the former, the media is changed in the familiar manner by the infiltration of a shiny and homogenous mass; degeneration is spread throughout the organ.

The follicles are generally large. Many still appear uninvolved, only isolated capillary vessels with amyloid walls are seen between the cells. In the afflicted bodies, degeneration usually is limited to the peripheral layers.

Here the capillaries are at times involved in extensive dilation, amyloid layers and cones are found between the lymph cells.

Less frequently the peripheral parts of the follicle are normal, while an irregularly shaped lump of shiny substance is noted in the middle. As a rule the latter has a dense consistency and shows only isolated cellular infiltrations.

Concerning the central artery, no fast rule may be established. At times it appears quite normal, at times involved.

The larger veins, the trabeculae, the reticulum are unchanged; the hyperplastic pulpa generally does not take part in deterioration. The wall of the capillary veins is changed into a narrow, glistening layer only in the close proximity of follicles, topped by unaltered endothelial cells.

Generally the described masses take the usual iodine-red color upon addition of diluted iodine solution; it is frequently deepened on the arteries by sulfuric acid, transformed to dirty blue or blue-grey hues on the layers and cones.

However, a more precise study of the preparations now reveals that all of the substances that seemed amyloid prior to the use of the indicated reagents, may not really be designated as such.

One notes at many points that the shiny masses deposited in the wall of the median arteries of the pulpa have taken only the yellow hue of the normal tissue. Hyaline and amyloid cross-sections lie close together; the same artery shows aggregations on one half of the tube with blue or red stains, a morphologically indistinguishable thickening on the other half with a pure yellow color. Frequently only the innermost layers of the altered vascular wall show the iodo-sulfuric acid reaction, farther out hyaline lumps and drops are deposited; hyaline rings are spelled almost regularly by amyloid ones; blue, red, yellow inspissations merge directly in some vessels.

The arteries within the follicles are now hyaline, now amyloid.

Transitions from colorless layers to stained, hyaline lumps next to dark blue tinted amyloid matter were also seen, although rarely.

This connection was more distinct in a second case, in which degeneration had progressed further. It affected primarily the follicles, which were strongly enlarged and usually completely changed to amyloid substance. In addition, others showed the earlier stages of degeneration: Amyloid capillaries, waxy, glistening layers in the peripheral parts. In some bubbles, larger homogenous lumps were deposited in the center.

Several zones are normally differentiated in the follicles, which resemble soaked kernels of sago.

In the middle (often next to the artery) there is a uniformly homogenous mass. Within it are scattered erythrocyte-containing capillaries, but as a rule a delicate system of communicating, fine fissures, at the junctions of which there are cellular elements.

This substance is enclosed by an intricate network of thick trabeculae, at times narrower, at times wider, which gradually fuses with

the normal tissue of the pulpa. Its mesh contains lymph cells and cellular particles.

Within the amyloid tissue, large and small hemorrhages are frequently noted.--

The arterial vessels which traverse the follicles are, in the majority of cases, intact; glossy deposits are found only in the median layer.

In the pulpa, too, affected arteries are rarely found.

When the organ sections are treated with iodine, iodo-sulfuric acid or iodine green, the picture becomes sufficiently colorful.

For one, arteries are seen (as in the previous case) which reveal convolutions with amyloid and hyaline lumps; in addition, among the masses of blue, blue-green or red follicles, some may be seen that have absorbed the yellow color of iodine or have remained colorless after treatment with iodine green.

They are most frequently found within the center of follicles which have not yet completely succumbed to change. They are the layers or parts of the larger lumps bordering on the central arteries, scattered between the lymph cells which I have just mentioned.

Often the iodo-sulfuric acid reaction is missing also from parts of the grosser reticular substance located in the follicle's periphery.

The hyaline strata are situated next to or between the amyloid ones, hyaline trabeculae change directly to amyloid; at times a gradual attenuation of the hue from deep blue to light yellow is noted.

Morphological or physical differences prior to staining were absent in this case as in the previous one. The sections were of the same thickness at the pertinent points, and the reagents -- as far as this could be controlled -- had the identical effect.

The situation was different in the spleen of a 20-year-old person who had succumbed to rapidly progressing pulmonary TB.

It was a pronounced case of sago spleen. The follicles had everywhere been changed to large, transparent bodies; microscopic examination showed even the central parts as amyloid. However, the arteries on which the follicles were based proved to be of hyaline degeneration by the use of iodine and sulfuric acid. The shiny masses had their seat in the media and the adventitia; the inner membrane of the vessel was invariably unchanged. The adventitia showed amyloid lumps at very few points; only a few vessels were completely normal.

I have observed the merger of hyaline and amyloid degeneration in two additional, fresh cases of waxy degeneration of the spleen. However, I do not intend to fatigue the reader either with their exact description or a discussion of the question, so frequently ventilated, concerning the seat of amyloid. It is enough that the fact of the coexistence of these processes and the manner of their connection has been recorded.

Now, it may be asked, are not the hyaline parts of more recent origin than the amyloid? We know of a similar situation in connection with the stratified bodies of the prostate, of which the largest and oldest usually no longer reveal a iodine reaction.

These assumptions are negated primarily by the copious occurrence of hyaline masses in cases of commencing amyloid degeneration; the observations of Burow and Raehlmann also speak against them.

Burow (21) removed two small polyps from the larynx of an older man; several additional, quite similar growths were left in the larynx due to the difficulty of the operation. The patient died 7 years after the operation. The tumors had gained in size, as determined by anatomical examination; they were composed of glossy masses of distinctly amyloid reaction, while previously extirpated specimens had merely had the character of fibromas (Neumann).

Raehlmann (22) found in the course of consecutive partial excisions from a conjunctival tumor that amyloid degeneration had been preceded by a stage of hyaline degeneration.

While the first objection to the conclusiveness of our cases is thus eliminated, another consideration, more difficult to overcome, remains.

The combination of hyaline metamorphosis of the arteries and amyloid change in the follicular tissue just described, tends to lead everyone to the conclusion that a coincidental meeting of amyloid degeneration and chronic endarteritis had been involved here, and that the remaining cases, while showing coexistence, are not an expression of an interior connection between hyaline and amyloid degeneration.

I can exclude a complication with arteriosclerosis from the described observations; they were conducted with organs of youthful individuals whose arteries did not present the least alteration. Whether the conditions for the appearance of hyaline are essentially the same as for the development of amyloid, or whether the postulated affinity of these substances does not exist and their coexistence is based on chance, all this may be differentiated only by exact investigation of the incidence of hyaline degeneration in the spleen, on which we have very limited data.

Klein (23) observed hyaline metamorphoses in the arterial vessels in scarlet fever; at times these seemed so severe as to obstruct the passage.

Vallat (24) found similar deposits in the intima and media of the small arteries in the spleen of tuberculous persons. One often finds hyaline thickening of the inner membrane and shiny masses in the median skin in the splenic vessels of older persons in which the arteries of the remaining organs have also become sclerotic. The process metastasizes to the adventitia and hyaline lumps are finally found next to the capillaries in the interior of the follicular apparatus.

These changes are rarely seen in children and younger persons with normal vascular systems.

I saw alterations in several cases of diphtheria; as in the descriptions of Klein concerning scarlet fever, both secretions of hyaline into the lumen of the arteries and glassy inspissation of the media were involved.

I further found hyaline degeneration in a number of chronic diseases.

The pertinent observations are briefly extracted here.

1. Katherine F., 6, a weak child from a healthy family, had been under the care of Prof. E. Boeckel since the spring of 1884 because of periarticular abscesses on the right radiocarpal joint. In the summer of the same year, symptoms of fungous coxitis were noted, necessitating resection of the right hip joint in the following winter. A few days later the girl died of acute peritonitis, caused by suppuration progressing from the carious acetabulum to the pelvis.

The autopsy did not produce fresh tuberculous foci, but revealed isolated small caseous nodules in the apex of the right lung and in the bronchial glands, one each in a papilla of the right kidney and the spleen. The latter was very large, pale and flaccid. No other noteworthy changes were found.

2. Josef W., a 38-year-old carpenter, was trephined by J. Boeckel in 1874 due to a skull injury. He remained healthy until 1878, when several enlarged lymph glands of the axilla became purulent.

In early 1884 he fell ill with a fungous inflammation of the knee joint. The joint was resected in the fall of 1884. The leg was amputated in February 1885, since a definitive cure could not be effected. On the evening of the day of operation a severe secondary hemorrhage from the art. prof. fem. set in, to which the patient succumbed on the following day.

Section did not reveal macroscopically visible changes, other than high-grade anemia and slight pulmonary emphysema. The arteries were completely normal.

The spleen was very much enlarged, greyish-red, soft; the pulpa emerged slightly upon section. Very numerous, large follicles were noted. Microscopic examination revealed isolated giant cell tubercles

in addition to hyaline degeneration, to be discussed later. The remaining internal organs seemed unaffected.

3. Adolf N., 3, had had the symptoms of pleuritis for 2 months. Autopsy showed a left-sided empyema of unknown etiology; no abnormalities other than rachitis and anemia. The spleen was large, pale and flaccid, with distinct follicles.

4. Margarethe L., 46, long history of diabetes. Sudden death. Section: Small gangrenous focus in the right lung; commencing pleuritis. No change in the arteries. Spleen large, pale, follicles rather small; it contains a hyperplastic node.

5. 26-year-old Friedrich K., mentally deranged, refused nourishment in the last months of his life and became extremely emaciated. A few days before death, gangrene appeared in the toe tips of both feet. Upon section (Dr. A. Hoffmann) numerous small cavities were found in the apex of the right lung. The vascular system failed to show abnormalities; the nerve trunks of the lower extremities also were found to be completely normal.

The spleen was enlarged and relatively rich in blood; the follicles were recognizable.

6. Fritz e., 7, since January 1882 suffering from a left-sided coxitis, complicated toward the end of 1883 by an inflammation of the lower thoracic vertebrae. On 19 April 1885 death from exhaustion. Result of autopsy: High-grade anemia of the internal organs. Hyperplasia of the spleen. Splenic follicles barely visible.

7. Ignaz B., 17. Osteomyelitis. Duration of disease barely 3 months. Section: Extreme emaciation. Decubitus. Focus in the left tuber ischii, bilateral coxarthrocace. Spleen large, pale, with distinct follicles.

8. The groom Jacob A., 18, fell ill in July 1884 with the symptoms of a light pleuritis; he became bedridden toward the middle of November. Death occurred on 21 Feb. 1885. Results of autopsy: Right pyopneumothorax caused by the perforation of a small cavity. Isolated peribronchitic and caseous foci in the lung. A serous pleural exudate on the left. Spleen large, pale, follicles not visible.

Hyaline degeneration, in the cases described, involves the smaller arteries and the follicles.

In the former, the shiny substance is usually located in the media, which is considerably thickened by the infiltration of shapeless lumps. As revealed by transverse sections, they do not always encompass the entire extent of the artery. Often a considerable part of the circumference remains unaffected, the hyaline substance forms a crescent-shaped clasp.

It is generally quite homogenous and characterized as true hyaline by its reaction to acids, acid-fast stains and iodine solutions.

Frequently the infiltrated arterial parts are interrupted by sections in which the normal pattern of musculature is apparent. The vessel thus takes on an appearance resembling a rosary.

If the genesis of the process is observed in arteries whose media is just beginning to show signs of degeneration, hyaline drops are first seen in the musculature, often located next to a nucleus, which they distort or displace. They vividly recall those hyaline trabeculae and rings which under certain conditions are found in the organic muscles. Larger masses also occur. They fuse into plates in which the rod-like nuclei of the muscle fibers die.

I always found the epithelium and intima unchanged; hyaline lumps in the adventitia are not rare. They are usually connected to the degenerate median layer, at times an otherwise normal vessel seems to be fused into the hyaline masses for extended lengths.

Emanating from the latter, a glossy structure of trabeculae at times penetrates between the elements of Malpighi's bodies; more frequently the discussed metamorphosis occurs in follicles whose arteries seem very little affected.

The lymph cells are displaced by more or less numerous, larger and smaller hyaline lumps, hyaline streaks traverse the tissue, in which, under favorable circumstances, erythrocyte-containing capillaries may be observed.

The larger clumps are rounded in shape. They contain granules and fibrils, usually several star-shaped cells with fine tendrils. Such masses have a certain similarity to osteoid tissue.

While the larger deposits usually occupy the central parts of the follicles, the second case shows that peripheral layers are also particularly involved.

Faintly glossy, oval layers have infiltrated the cells; smaller, hyaline lumps, barely the size of lymph cells, seem to have fused to an irregularly shaped mass, having absorbed capillaries and residues of nuclei and cells.

Up to the region of the arteries, the alteration progresses in but a few follicles. In them, between the multitude of hyaline layers, there is only a narrow network of apparently unchanged leukocytes.

I deem it very probable that all of these hyaline masses owe their development to the protoplasm of the follicular cells. In support of this opinion, I enclose the picture of a follicular segment originating with case 4.

The majority of follicles in this spleen had those large-cell centers which I have described in the preceding chapter. The protoplasm of the cells (some without nuclei) frequently was homogenous, and the hyaline clumps scattered between them showed by the enclosed, neighboring or superimposed nuclei that in their place, too, the large cellular elements belonging to the nuclei had to be present originally.

In all cases hyaline degeneration was disseminated to such an extent that its pathological significance was beyond a doubt. In one, the arteries were predominantly affected, in another the follicles; even in drastically changed organs, normal follicles and arteries could still be found.

That a deposit of hyaline substances in preformed Malpighi bodies was really involved, and not a hyaline metamorphosis of tubercles, will surely be believed upon my assurance.

I add this note because Vallat, the only author who gives data on the occurrence of those masses in the spleen, has always felt obliged to consider them as transformed tubercles. He says (25): In both described varieties of tubercle, fibrin is found only in the tubercle proper and has no direct connection with the normal splenic tissue. However, foci of canalized fibrin may also be found in a third series of cases, wedged directly into the splenic tissue. Here the hyaline masses gradually melt into the normal tissue. Frequently giant cells are the only sign of tubercular character. (Incidentally, in these cases tubercles were always present in other organs).--

It is hardly necessary to point out the strong agreement of the hyaline changes described with the amyloid degeneration of the spleen with respect to morphology.

This is immediately apparent in the arteries, but even in the examination of Malpighi's bodies one must frequently resort to iodine in order to make the diagnosis.

Those frequently occurring hyaline lumps are indiffereniable from the homogenous masses that we met earlier in the sago spleen, at times as amyloid, at times only as hyaline parts, and in the second of the above-mentioned cases, entire follicles are encountered of which even an experienced observer could not say, without the help of reagents, whether amyloid or hyaline degeneration was involved.

The similarity does not only involve the form, however, but also the distribution of degeneration: In the arteries we invariably note that the median skin is affected first, in the follicles the larger clumps are located in the center, the deposit of smaller layers begins in the peripheral parts.

Upon examination of the described anamneses we recognize a common bond which ties the individual cases: Severe disturbances in nutrition, occurring as sequels to various diseases.

If the 4th and 5th cases are not considered (although waxy degeneration of the spleen has also been seen once in connection with diabetes, 26), the same affections that usually are accompanied by amyloid degeneration are obtained as the basis of these nutritional defects: Chronic inflammation of the bones and joints, chronically inflamed (tuberculous) lesions of the respiratory organs.

Most of the reported cases differ from the usual course of such diseases by their relatively short duration.

I should like to call particular attention to the first two histories.

Unexpected sequels to operative treatment terminated the patients' life; widespread degeneration was found in the spleen, corresponding to amyloid according to form and dissemination, but showing a hyaline reaction. These cases, precisely, prove that the conditions for the development of hyaline are very similar to those that favor the appearance of amyloid. They may almost be considered experiments, interrupted at a time when the chemical transformation of the hyaline substance to amyloid had not yet been completed.

If the requirements considered necessary for the proof of a connection between hyaline and amyloid degeneration are met thereby, one is tempted to use these investigations for the postulation of a complete theory of amyloid degeneration.

One could conclude that the described chronic diseases had caused a regenerative hyperplasia of the spleen, but that further development of newly formed cells was inhibited, that they degenerated into hyaline masses due to insufficient nutrition. At the same time, possibly caused by the feverish conditions connected with those diseases, hyaline degeneration would appear in the arterial musculature, which in turn would be able to exert an unfavorable influence on the organ's nutrition.

We ought not to be overly embarrassed by questions about the circumstance that hyaline in the spleen later changes to amyloid, while ordinarily (e.g. in the tubercle) such a metamorphosis never occurs.

We would point out that those organs, though pale in appearance, still contain rather copious amounts of blood.

Hyaline and amyloid masses as a rule are enclosed by filled capillaries, even smaller or larger hemorrhages within amyloid follicles are not rare. It is precisely this constant contact with the blood, making possible the suspected influence of one of its components on the altered protoplasm (the hyaline substance), in which the real reason for its final transmutation to amyloid ought to be found.

I appreciate full well how far such a plausible opinion is removed from complete certainty.

For one, the indicated theory completely ignores the amyloid degeneration of the pulpa; secondly, strictly speaking, the underlying observations merely prove that the development of hyaline must be accompanied by circumstances that are similar to those found in the genesis of amyloid.

If both substances are found at the same time, if this form of degeneration is found in one case and an identical case reveals another form, it is permissible to deduce the close relationship of these processes. However, no proof is established thereby of the theory that one substance represents the necessary preceding stage of the other.

This proof can be submitted only when it becomes possible to generate amyloid degeneration experimentally; only then shall we be able to determine the preceding tissual changes with greater certainty than has been possible by the comparison and investigation of historic cases.

NOTES.

- (1) Cf. the summarizing presentation in Cellular Pathology, 1871, p. 437 ff.
- (2) Cohnheim, Manual of general Pathology, 1877. I. p. 570.
- (3) Virchow, loc. cit. Kyber, this archive, Vol. 81, p. 436.
- (4) Cohnheim, loc. cit. (5) Manual of General Pathology. p. 417.
- (6) Contributions to pathological Histology, p. 184. (7) This archive, Vol. 13, p. 95. (8) Tumors II, p. 26. (9) Archive for Ophthalmology X.
- (10) This Archive, Vol. 94, p. 289. (11) Manual of Pathological Anatomy, 3rd ed. p. 90. (12) Deutsche Zeitschrift fuer Chirurgie, XXII, p. 30.
- (13) Cases by Ziegler (this Archive, Vol. 65), Lesser (Vol. 69) and Balser (Vol. 91), as well as Th. Leber's investigations (Graefe's Archive XXV) should also be mentioned. (14) This Archive, Vol. 54. (15) Inaug.-Diss. Kiel 1881. (16) This Archive, Vol. 72, p. 506. (17) This Archive, Vol. 81. (18) This Archive, Vol. 81, p. 3. (19) This Archive, Vol. 79, p. 556. (20) Loc. cit. p. 404. (21) Langenbeck's Archive XVIII, p. 242.
- (22) This Archive, Vol. 87, p. 331. (23) Transact. of the pathol. soc. 28, p. 430. (24) This Archive, Vol. 89, p. 211. (25) Loc. cit. p. 206.
- (26) Frerichs, On Diabetes, p. 141.